



A REVIEW OF THE INCIDENCE, CHALLENGES & TREATMENT OF ALZHEIMER'S DISEASE IN INDIA WITH SPECIAL EMPHASIS ON THE USE OF AYURVEDIC AND HERBAL MEDICINE

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ABSTRACT

The incidence of Alzheimer's disease in India has always posed unique challenges owing to the dynamic demography of the nation, along with other socioeconomic, cultural and environmental factors. This is further exacerbated by the lack of knowledge regarding the pathogenesis of the disease. The lack of infrastructure, economic constraints, and diagnostic difficulties - form a pivotal part of the challenge. This paper carried out a systematic review to evaluate, analyze and summarize patterns and trends in existing literature while mapping knowledge gaps to propose potential areas of future research. Herbal drugs, through preclinical and clinical trials, have been found to have significant therapeutic potential. While the incidence of AD was found to be the highest in Jammu and Kashmir and in Odisha, lack of awareness and studies about the disease in India result in sparse information. Preclinical trials also suggest huge potential for Ayurvedic medicine. However, the lack of clinical trials in most medicines suggests that these still require intensive study before being ready for human use. It still seems a long way before Alzheimer's can be expected to take a positive turn in India.

KEYWORDS: Alzheimer's Disease, Diagnostic Difficulties, Systematic Review, Ayurvedic Medicine, Herbal Medicine, Cognitive Decline, Pathogenesis, Therapeutic Potential

INTRODUCTION

Discovered by clinical psychiatrist Alois Alzheimer in 1906, Alzheimer's disease is the most common form of dementia. Attacking neurons in the hippocampus and the entorhinal cortex before destroying further connections, is responsible for debilitating language, thinking, speech, behavior, and eventually an individual's consciousness of their environment. The burden of Alzheimer's remains checkered across continents and nations. Nonetheless, it is no secret that neurodegenerative disease disproportionately affects middle and low - income countries.

India, being a lower-middle-income nation, is vis-a-vis a huge Alzheimer's dilemma in 2023. Challenges in India range from a lack of awareness among the general population, social taboos, language and cultural barriers, economic constraints, caregiver burden, and limited access to healthcare among others.

These further exacerbate the problem, resulting in a disproportionate incidence of Alzheimer's disease. Dementia research in India also poses unique challenges such as the need to adapt cognitive tests (most of which were originally developed in English-speaking countries for literate individuals) to the sociocultural context²⁴, while taking into account the fact that large sections of the population have low levels of literacy. Although some cognitive tests, such as the Addenbrooke's Cognitive Examination (ACE-III), have been translated and adapted to Indian languages²⁵, the relevance of such tests among illiterate populations is a matter of debate. A neurocognitive test battery called the Indian Council of Medical Research-Neurocognitive Tool Box (ICMR-NCTB) was developed in India for use among literate and illiterate individuals. This paper will examine the thesis that *challenges related to Alzheimer's in India have been further exacerbated over the previous decade due to an increase in population*. The paper will begin by evaluating recent Alzheimer's studies taken up in regions of India followed by a detailed analysis of the challenges related to the disease in India ranging from lack of awareness, stigma and misconceptions, and lack of infrastructure among others. This will be followed by an evaluation of the current treatments for Alzheimer's in India with special emphasis on Indian medicine and recent innovations.

LITERATURE REVIEW

Recent years have seen an upsurge in the number of Alzheimer's studies taken up across India. Nonetheless, research in this field remains significantly low with most studies having been conducted years ago, thus not reflecting the current landscape in their conclusion. A chronological review of previously conducted Alzheimer's studies in India are a prerequisite to carrying out further analysis.

An Indo - US Cross-National Dementia Epidemiology Study was conducted in a rural elderly Hindi-speaking population in Ballabgarh in northern India, the overall prevalence rate for AD was 0.62% in the population aged 55+ and 1.07% in the population aged 65+. Greater age was associated significantly with a higher prevalence of both AD and all dementias, but neither gender nor literacy was associated with prevalence. The study also focused on finding the practical issues of cognitive screening. Its objectives included determining the prevalence of the disease while comparing these results with those found in a defined American community (Chandra et al., 1998). The relevance of the study in this

century is questionable considering that several factors have changed since then. A study to estimate the prevalence of dementia in a rural population in a community located on the outskirts of the city of Madras in South India, interviewed people using the Geriatric Mental State Schedule (GMS). The prevalence of dementia was found to be 3.5%, the percentage increasing with age. These rural prevalence estimates were higher than in urban settings, signaling a pattern in Alzheimer's incidence in the country (WHO multicentre study on cognitive impairment and dementia in developed and developing countries, unpublished) (1997 John Wiley & Sons, Ltd.).

The potential of Indian medicine for Alzheimer's disease has been subject to critical research in India.

Several herbal medicines including Centella asiatica, Evolvulus alsinoides and Bacopa monnieri, Desmodium gangeticum have been considered to be useful. Curcumin, the phytochemical agent in the spice turmeric, which gives Indian curry its yellow color, is a traditional Indian medicine. A study on Curcumin in 2011, demonstrated that curcumin could target pathways involved in the pathophysiology of Alzheimer's Disease (AD), such as the β -amyloid cascade, tau phosphorylation, neuroinflammation or oxidative stress. These findings suggest that curcumin might be a successful compound for the development of AD therapy. However, its insolubility in water and poor bioavailability have limited clinical trials and its therapeutic applications. To be effective as drug therapy, curcumin must be combined with other drugs or new delivery strategies need to be developed. (Belkacemi et al., 2011).

A 2015 study on the Preventive Role of Indian Black Pepper in Animal Models of Alzheimer's Disease used 24 rats and found a marked decrease in cholinesterase level, amyloid plaque formation in rats' brains who were pretreated with piper nigrum. At the same time there was a decrease in escape latency time (ELT) and an increase in memory in piper-treated rats. This study confirmed how this technique could be tested on large populations while further research on cholinesterase inhibitors and the role of flavonoids in the prevention of neurodegeneration in Alzheimer's disease could be encouraged (Subedee L, et al. 2015).

A case study by Jigeesh P. P. et al. (2019) followed the treatment of a 74-year-old woman with Advanced Alzheimer's disease using Ayurvedic medicine. The treatment combined appropriate panchakarma procedures and selected Ayurveda drugs. The patient's condition was assessed before and after treatment using a Dementia Severity Rating Scale (DSRS) in which improvement in her motor activity, and retardation of progression of symptoms without any adverse effect were noticed. Such case studies demonstrate ideas for a line of treatment to be employed for similar cases in the future.

A 2022 study found that the estimated dementia prevalence for adults ages 60+ in India is 7.4%, with significant age and education gradients, sex and urban/rural differences, and cross-state variation. The study also recognizes the need for a nationwide study of dementia that captures the diversity of the country. According to the India State-Level Disease Burden Initiative collaborators, the magnitudes of disease burden and risk factors vary significantly across the

country, with the state of Kerala exhibiting better health indicators than the rest of India for the past several decades. (Lee, J, Meijer, E, Langa, KM, et al. 2022).

All aforementioned studies are evidence that represents the diverse demography of India and varying effects subject to a range of auxiliary factors.

METHODOLOGY

A secondary qualitative research method was used for this paper since the focus was on herbal and ayurvedic medicine. A systematic review of this question aims to synthesize the results of studies conducted on Alzheimer's disease in India.

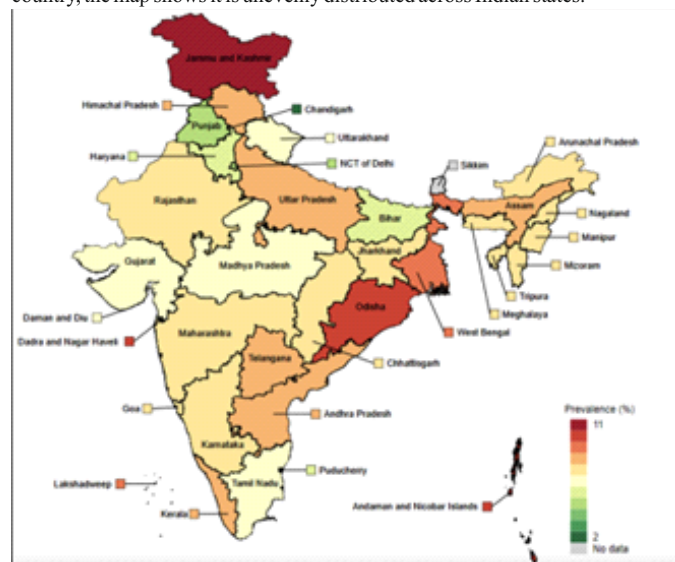
Studies for the review have been selected after an analysis of the scope of the studies and their emphasis on challenges and treatments unique to India. Studies range from 1995 to 2023 - encapsulating the developments made in the most recent decades where significant research was undertaken. To get a complete picture covering all economic strata, a combination of studies conducted both in rural and urban settings have been selected. Studies on Ayurvedic medicine have been chosen after careful consideration of their administration of preclinical and clinical trials. A striking observation was the lack of accounts from Alzheimer's affected families, which can be beneficial for several patients and caregivers. Results and conclusions of several studies concerning Ayurvedic treatment have been tabulated to provide a comprehensive summary for the same while challenges have been dealt with primarily through Qualitative Analysis (verbal accounts, interviews, caregiver experiences). The qualitative analysis has been conducted from a range of credible sources in order to draw accurate and reliable conclusions. Conclusions have been drawn on the basis of the qualitative data collected, helping answer questions under the scope of this review.

RESULTS

Incidence of Alzheimer's disease in India

Image courtesy of Dr. Jinkook Lee. Dr. Lee is a Senior Economist, and Director, Program on Global Aging, Health, and Policy at the University of Southern California.

Map showing the prevalence of dementia by state in India with dark red signifying the highest prevalence and dark green the lowest. While 7.4% is the estimated dementia prevalence rate for adults aged 60 and older across the country, the map shows it is unevenly distributed across Indian states.



The highest incidence of 11% was found in Jammu and Kashmir and Odisha. States with the least prevalence were Punjab and Bihar.

Interviews and Verbal Accounts

Sarmishtha Dutta Gupta from India for Alzheimer's Disease International's '2021 World Alzheimer's Month campaign' talked about her first-hand experience as her mother was diagnosed with vascular dementia. She highlighted how when she started noticing symptoms and also faced challenges due to social taboos and mindset regarding the truth about vascular dementia. She elaborated upon how no one believed her when she told them about the possibility of the disease while she was alone and did not have any support system or organizations due to a lack of awareness surrounding the disease.

Another interview noted: I was stunned and overwhelmed when I was told that I would have to take Ma back home in that helpless state with traction and tubes sticking out of her, and that I would have to take care of her at home. I had no idea what such care involved. She had a Ryles tube in her nose, a catheter and a traction (Dementia Care Notes).

The woman is a chartered accountant who left her job to take care of her mother-in-law.

A large mismatch in the knowledge and understanding of dementia among the caregiver in a carefully designed study raised serious concerns. (Narayan et al, 2015). One interview question directly inquired "What do you think is happening to your family member?" Only 4 of the respondents described the situation in a way that reflected a clear understanding of the progression of dementia ("Alzheimer's is an irreversible progressive brain disease"). 12 described the situation only in terms of memory and forgetfulness and provided no indication that they understood the disorder to be a problem of global cognition that might be affecting either behavior or day-to-day functioning.

Indicating the systemic issues in India, such interviews illustrate the pivotal problem of a lack of awareness about the disease. With family members not being fully equipped with all the knowledge required to care for a patient at home, such circumstances can become challenging and become a burden on families, further hindering the caregiving process. All family members of an Alzheimer's patient must be fully made aware of all aspects of the disease, helping them provide the best possible care for the patient.

Comprehensive Review of Ayurvedic and Herbal Medicine

Nervous system disorders, also known as 'VataVyadhi' in Sanskrit, was thought to be brought on by imbalances of Vata, the biological air humor, essentially the energy that moves through the brain and the nerves controlling both voluntary and involuntary functions. Therefore, Vata derangements always involve some weakness, disturbance, or hypersensitivity of the nervous system (Rao et al. Alzheimer's Research & Therapy 2012).

Following is a summary of a few Ayurvedic medicines which have been studied for some time and are in the process of being tested currently.

S. No.	Medicine	Family, Uses, biological specifics	Preclinical Studies	Clinical Studies
1.	Bacopa monnieri (Brahmi)	Scrophulariaceae family	An alcoholic extract of B. monnieri improves acquisition, consolidation, and retention of memory in the foot shock motivated brightness discrimination test, active conditioned avoidance test and Sidman continuous avoidance responses in rats (Mehla et al. 2020).	A six-week Bacopa administration (300 mg for subjects under 90 kg, and 450 mg for subjects over 90 kg, in a double-blind, randomized, placebo-controlled fashion has been associated with significant improvement in the retention of new information in 40–65-year-old healthy adults
2.	Curcuma longa (Turmeric)	Zingiberaceae family - used as a food flavoring and coloring dye in India The problem of water solubility for turmeric has been solved by the synthesis of biodegradable poly (lactic-co-glycolic acid) (PLGA) coated curcumin nanoparticles.	Shown to reduce both in-vivo and in-vitro Aβ plaque deposition, Curcumin treatment for six months significantly decreased the elevated levels of oxidized protein and proinflammatory interleukin-1β in the transgenic APPSw mouse brain (Tg2576). Plaque formation and the concentration of insoluble and soluble Aβ were also lowered by curcumin in the same study.	Lack of clinical data on the use of Curcuma longa
3.	Clitoria ternatea	Fabaceae family	Rai et al. have described the learning and memory-enhancing effect of the C. ternatea root extract during the growth spurt period in rats. They intubated 7-day-old neonatal rats and administered 50 and 100 mg/kg of the aqueous root extract of C. ternatea for 30 days.	The medicine has still not been evaluated for human use.
4.	Withania somnifera (Ashwagandha)	Solanaceae	Treatment with Withania root extract (1 g/kg, p.o	A prospective, randomized, double-blind,

			for 30 days) has been found to reverse the AD pathology by upregulating the low-density lipoprotein receptor-related protein, by enhancing the Aβ clearance and ameliorating the cognitive deficit in middle-aged and old APP/PS1 mice	A prospective, randomized, double-blind, placebo-controlled study reported that treatment with ashwagandha-root extract (300 mg twice daily for eight weeks) improved immediate and general memory functions and enhanced executive function, attention and information processing speed in adults with a mild cognitive impairment In a systematic review, Ng and colleagues have also mentioned that W. somnifera extract ameliorated cognitive impairment and improved executive functions in adults with mild cognitive impairment.				
5.	Centella asiatica (Gotu kola)	Apiaceae	Dhanasekaran et al. have found that an 8-month treatment with 2.5 mg/kg of aqueous extract of C. asiatica significantly decreased amyloid beta 1-40 and 1-42 level in the hippocampus of PSAPP transgenic mice expressing “Swedish” amyloid precursor protein and M146L presenilin 1 mutations, which result in spontaneous amyloid beta plaque formation.	In a randomized, double-blind placebo-controlled, study, C. asiatica extract was administered to healthy volunteers at 250–750 mg once daily dose for 2 months. The high dose enhanced working memory and improved self-rated mood				
6.	Celastrus paniculatus (Jyotishmati)	Celastraceae, C. paniculatus	A study by Raut et al. 2015, has found that amnesic Mice receiving C. paniculatus showed significant memory enhancement as compared to scopolamine group. The effect of C. paniculatus and the combination of C. paniculatus with piracetam was comparable to that with piracetam alone.	C. paniculatus has not undergone clinical trials due till date.				
7.	Desmodium gangeticum	Fabaceae	Joshi et al. (2006) found that pretreatment with DG (50, 100, and 200 mg/kg p.o.) for seven successive days significantly improved learning and memory in mice and reversed the amnesia induced by both, scopolamine (0.4 mg/kg, i.p.) and natural aging. DC also decreased whole brain acetylcholinesterase activity.	Clinical evidence is not available to date.				
8.	Moringa oleifera	Moringaceae - has been used to clarify water due to its coagulant property	A study by Hossain et al. (2022) used Wistar rats having 150–250 g bodyweight and divided them equally into three groups: Group-I/normal memory group (treated with oral normal saline 5 ml/kg body weight), Group-II/memory-impaired group (induced by intraperitoneal ketamine 15 mg/kg body weight), and Group-III/experimental group (treated with oral Moringa oleifera 200 mg/kg body weight and intraperitoneal ketamine 15 mg/kg body weight). The experimental group showed significantly fewer working memory errors than the memory-impaired group. The experimental group also provided the lowest variability of WMEs among groups					Clinical evidence is not available to date.
9.	Convolvulus pluricaulis (Shankhpushpi)	Convolvulaceae	The ethanolic extract of C. pluricaulis and its ethyl acetate and aqueous the fraction at the dose of 100 and 200 mg/kg, p.o showed memory-enhancing properties in Cook and Weidley's Pole Climbing Apparatus, passive avoidance paradigms, and active avoidance tests.					Clinical evidence is not available to date.

DISCUSSION

Incidence of Alzheimer's disease in India

The Alzheimer's Association developed the first national study of dementia in India, the Harmonized Diagnostic Assessment of Dementia for the Longitudinal Aging Study in India (LASI-DAD; N = 4096). The study's results observed that Alzheimer's incidence shows a strong age gradient, with prevalence sharply increasing with age. While women are almost twice likely to get affected, AD is also much more common in rural and urban areas. It is also considerably more prevalent among individuals with lower education.

Cross-state variation in dementia prevalence is considerable, with the lowest prevalence in Delhi at 4.5% (95% CI, 1.9 to 7.1) and the highest in Jammu and Kashmir at 11.0% (95% CI, 7.3 to 14.8). An increase from 8.8 million individuals aged 60 and older with dementia in 2016 to 16.9 million in 2036 can be expected. The differences can stem from varying levels of educational attainment across states along with variations in dementia risk factors such as undernutrition, uncontrolled cardiovascular disease, and exposure to indoor air pollution.

The current rising trend is certainly troublesome and indicates the urgent need for more frequent studies on AD prevalence in India, particularly in rural regions.

Challenges related to Alzheimer's disease in India

Language barriers form a major challenge, as most people in rural India are non-English speakers, and a robust testing system is driven by the elimination of the language constraint. Transport is also a challenge as traveling large distances is not economically possible for a majority of the Indian population. At-home tests and surveys are generally preferred over having to travel. Late prioritizing of healthcare remains a significant problem, which stems from a lack of understanding of the disease. The study by Narayan et al. (2015) highlights how this gap in understanding can affect the care of Alzheimer's patients, giving rise to misconceptions. Most importantly, socio-economics difficulties exacerbate these problems while insufficient resources at patients' homes lead to them not

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getting the best possible care. There is an urgent need for low-cost centers for patients, where they can stay for a long time, aided by nurses and other professionals.

Use of Ayurvedic and Herbal medicine as potential treatment

All medicines included in this paper have undergone preclinical trials which reveal that they have healing properties including catalyzing memory retention and inhibiting amyloid beta formation. *B. monniera*'s standardized extract, for example, involves the microRNA 124-CREB pathway and serotonergic receptor in the memory-enhancing mechanism (Mehla J et al, 2020).

It has been found to enhance protein kinase activity and increase the protein content in the hippocampus, which may also contribute to their memory-enhancing effect. All loopholes in medicines have also been addressed through the use of mechanisms including nanoparticles.

One of the most concerning challenges, however, is that several of these medicines have not been taken to the clinical phase due to a lack of systematic evaluation, research, and initiative for the use of Ayurvedic medicine in Alzheimer's.

CONCLUSION

Alzheimer's in India is a disease that still has multitudes of unaddressed aspects. Even the aspects which have been studied require higher level research, subject to the status of India as the soon-to-be most populated country in the world. Similarly, Ayurvedic medicine is a diverse field that has shown positive results in the past. It is important to now draw upon these results. This paper aims to highlight this topic and the various gaps in its research which need to be addressed by the medical community. Clinical trials of various drugs with curing potential need to be carried out while further quantitative research should also be conducted to validate the findings of the qualitative research.

Other areas of research which can be taken up to enhance our understanding of Ayurveda can include **genetic modeling of Ayurvedic medicines to precisely identify their genetic component and its comparison with the risk-causing genes of Alzheimer's** which include Amyloid Precursor Protein (APP), PSEN 1 and PSEN 2. Such studies can go a long way in demystifying the challenges of Alzheimer's disease, providing us with more detailed and concrete answers for our next steps forward.

After a thorough evaluation of all sections of the paper, it can be concluded that challenges related to Alzheimer's have been exacerbated over the previous decade. Nonetheless, this effect is because of several factors and not only the increasing population of the country. It should also be noted that there are certain Ayurvedic remedies that are currently prescribed. Trailokya Vijaya Vati is one such potent and effective Ayurvedic medicine. Ayurvedic doctors highly prescribe it because it can effectively alleviate Alzheimer's symptoms and improve overall both mental health and function among patients. More of such remedies is the need of the hour as we inch closer to times when Alzheimer's incidence is expected to rise rapidly.

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